

Welcome to today's FDA/CDRH Webinar

*Thank you for your patience while additional time is
provided for participants to join the call.*

**If you have not connected to the audio portion of the
webinar, please do so now:**

U.S. Callers Dial: 888-324-9236

International Callers Dial: 1-415-228-3923

Passcode: 2798264

Clinical Laboratory Improvement Amendments of 1998 (CLIA) Waiver Applications Draft Guidances

Peter Tobin, Ph.D.
Chemist

Division of Program Operations and Management
Office of In Vitro Diagnostics and Radiological Health

Center for Devices and Radiological Health

This Webinar Covers Two Complementary Draft Guidances for CLIA Waiver Applications:

- Select Updates for Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices
 - Referred to as: Draft “Section V” Guidance
- Recommendations for Dual 510(k) and CLIA Waiver by Application Studies
 - Referred to as: Draft “Dual” Guidance
- **These draft guidances are not final and not in effect at this time**

Agenda

- Background
- Revised Draft Section V Guidance
- Revised Draft Dual Guidance

Objectives

- Understand CLIA waiver pathway options:
 - CLIA waiver application following clearance or approval
 - Dual Submission (Combined 510(k) and CLIA waiver application following a pre-submission)
- Understand the FDA's current thinking on study designs for both pathways

Background

- CLIA waiver statutory criteria
- 21st Century Cures requirements to update the 2008 CLIA Waiver Guidance
- CLIA waiver pathways addressed by the two drafts
- Why we are re-issuing the guidances as drafts

CLIA Statutory Criteria for Waiver

CLIA, 42 U.S.C. 263a(d)(3) Examinations and Procedures, as modified by the Food and Drug Administration Modernization Act of 1997 (FDAMA):

“The examinations and procedures [that may be performed by a laboratory with a Certificate of Waiver]... are laboratory examinations and procedures that have been approved by the Food and Drug Administration for home use or that, as determined by the Secretary, are simple laboratory examinations and procedures that have an insignificant risk of an erroneous result, including those that –

A) employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible, or

B) the Secretary has determined pose no unreasonable risk of harm to the patient if performed incorrectly.”



21st Century Cures Requires an Update to Sec V. of the CLIA Waiver Guidance

- Sec. 3057, CLIA Waiver Improvements, requires the FDA to publish guidance that:
 - (1) revises “Section V. Demonstrating Insignificant Risk of an Erroneous Result – Accuracy” of the [2008 CLIA Waiver Guidance*]
 - (2) includes the appropriate use of comparable performance between a waived user and a moderately complex laboratory user to demonstrate accuracy.

[* Recommendations for Clinical Laboratory Improvement Amendments of 1988 \(CLIA\) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices](#)

Summary of 2008 CLIA Waiver Guidance



- **Is the test system simple?**
 - Simple test characteristics
 - Labeling for waived users (for example: Quick Reference Guide at 7th grade level)
- **Does the test system have an insignificant risk of erroneous result?**
 - Risk Analysis
 - Flex Studies
 - Accuracy Studies

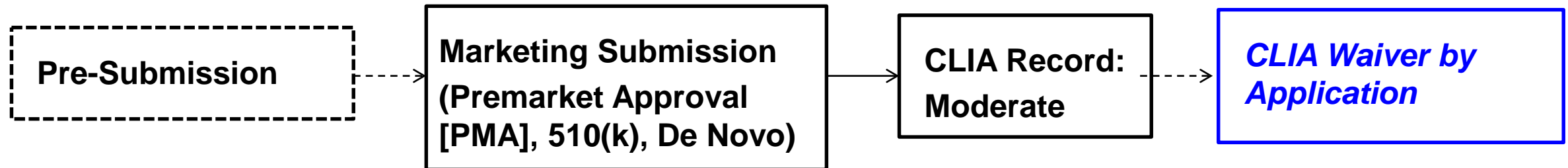
The Draft Guidances Address Two CLIA Waiver Pathways



CLIA Waiver by Regulation or Clearance for Home Use



Stepwise CLIA Waiver by Application *(2008 CLIA Waiver Guidance & Draft Section V)*



Dual 510(k) and CLIA Waiver by Application *(Draft Dual Guidance)*



Re-Issuing Significantly Revised CLIA Waiver Guidances in Draft to Allow Stakeholder Comments



- Previous drafts of both guidances were issued in November 2017
- Based on comments received, and multiple meetings with stakeholders, the new drafts have been thoroughly revised
- Because of the significant changes made, we are re-issuing in draft to allow stakeholder comments before finalizing

Definitions

- *Untrained Operator or Waived User:*
 - A test operator in waived settings who has limited or no training or hands-on experience in conducting laboratory testing.

- *Trained Operator or Moderate Complexity Laboratory User:*
 - A test operator who meets the qualifications to perform moderate complexity testing (42 CFR 493.1423) and with previous training in performing the test.

Revised Draft Section V Guidance

- Provides study design recommendations for demonstrating that a test is accurate in the hands of intended CLIA-waived users
 - as part of a CLIA waiver application following clearance/approval
- The FDA believes this guidance will reduce barriers to bringing simple and accurate tests to CLIA-waived settings, such as doctor's offices

The Revised Draft Section V Focuses on Study Design Aspects Directly Related to Meeting the Statutory Criteria for CLIA Waiver



- Emphasizes validating that the accuracy of a candidate test is not meaningfully impacted by differences between non-waived and waived use, including:
 - user training and experience,
 - testing environment, or
 - patient populations
- General information on test accuracy issues not specific to CLIA-waived tests has been replaced with references to FDA-recognized consensus standards
 - Additionally, examples of successful CLIA waiver study designs can now be found in publicly posted CLIA Waiver Decision Summaries

CLIA Waiver Decision Summaries Promote Consistency and Predictability



Home > About FDA > FDA Organization > Office of Medical Products and Tobacco > About the Center for Devices and Radiological Health > CDRH Transparency

CDRH Transparency

CLIA Waiver by Application Decision Summaries

Test System Name	Document Number	FDA Review Decision Summary	Effective Date (DD/MM/YYYY)
Nova Biomedical StatStrip Glucose Hospital Meter System	CW180005	CW180005.pdf Decision Summary	07/12/2018
Cepheid Gene Xpert Xpress System (Xpert Xpress Strep A)	CW170014	CW170014.pdf Decision Summary	04/26/2018
Alere i System (Alere i Influenza A & B 2)	CW170013	CW170013.pdf Decision Summary	03/23/2018
Mesa Biotech Accula Flu A/Flu B Assay	CW170007	CW170007.pdf Decision Summary	02/06/2018
ACON Laboratories Inc., Mission Cholesterol Pro Monitoring System {Mission Cholesterol Pro Test Cartridges}	CW170010	CW170010.pdf Decision Summary	01/19/2018

Additional Study Design Options Provide Flexibility

- Option 1: Agreement Studies
 - Comparison study designs in which the results of the candidate test in the hands of untrained operators are compared to the results of the candidate test in the hands of trained operators
 - The FDA believes Option 1 will be appropriate for the majority of candidate tests
- Option 2 (**New**): Agreement studies modeled after approaches in the FDA guidance on [Assay Migration Studies for In Vitro Diagnostic Devices](#)
- Option 3 (**New**): Flex and human factors engineering studies
- Option 4: Direct Comparison to an Appropriate Comparative Method
 - Comparison study designs in which the results of the candidate test in the hands of untrained operators are directly compared to the results of an appropriate comparative method in the hands of trained operators.

We're Harmonizing Our Approach to CLIA Waiver Benefit-Risk Considerations with Other FDA Benefit-Risk Guidances



- All tests have some likelihood of erroneous results, but whether the likelihood of erroneous results in the hands of waived test users is negligible will vary from test to test depending on a number of factors, including:
 - intended use,
 - context of use (for example: patient population, use environment),
 - probable benefit(s) and probable risk(s) or harm(s) associated with waived use of the test
- Accordingly, the appropriate acceptance criteria for CLIA waiver accuracy studies will vary from test to test
- For details about the FDA's current thinking about benefit-risk considerations for medical devices, CDRH benefit-risk guidances are referenced rather than repeating similar material

General CLIA Waiver Study Design Considerations Have Not Changed



- The FDA recommends that applicants evaluate test performance in settings designed to replicate, as closely as possible:
 - intended CLIA-waived settings
 - patients/samples,
 - test operators, and
 - testing over time, as in the typical intended use setting
- [Pre-Submissions](#) are highly recommended to get feedback from the FDA on study designs before conducting the studies

Revised Draft Dual Guidance

- Describes a more efficient single set of comparison and reproducibility study designs with untrained users for a Dual Submission
- Similar to Section V, general information on test accuracy issues not specific to CLIA-waived tests has been replaced with references to FDA-recognized consensus standards
- The FDA believes the Dual pathway is in many instances the least burdensome and fastest approach for manufacturers to obtain a CLIA waiver in addition to 510(k) clearance for new tests

Historically, Separate 510(k) and CLIA Waiver Studies Have Been Conducted in Different Clinical Settings

510(k)	Point of Care (POC) Sites & Trained Users
CLIA Waiver by Application	Waived Sites & Untrained Users

- In this two step approach, manufacturers conduct separate comparison and reproducibility studies, in different clinical settings, first to support 510(k) clearance and later to support CLIA Waiver by Application.

The Dual Approach Provides Time and Study Efficiencies

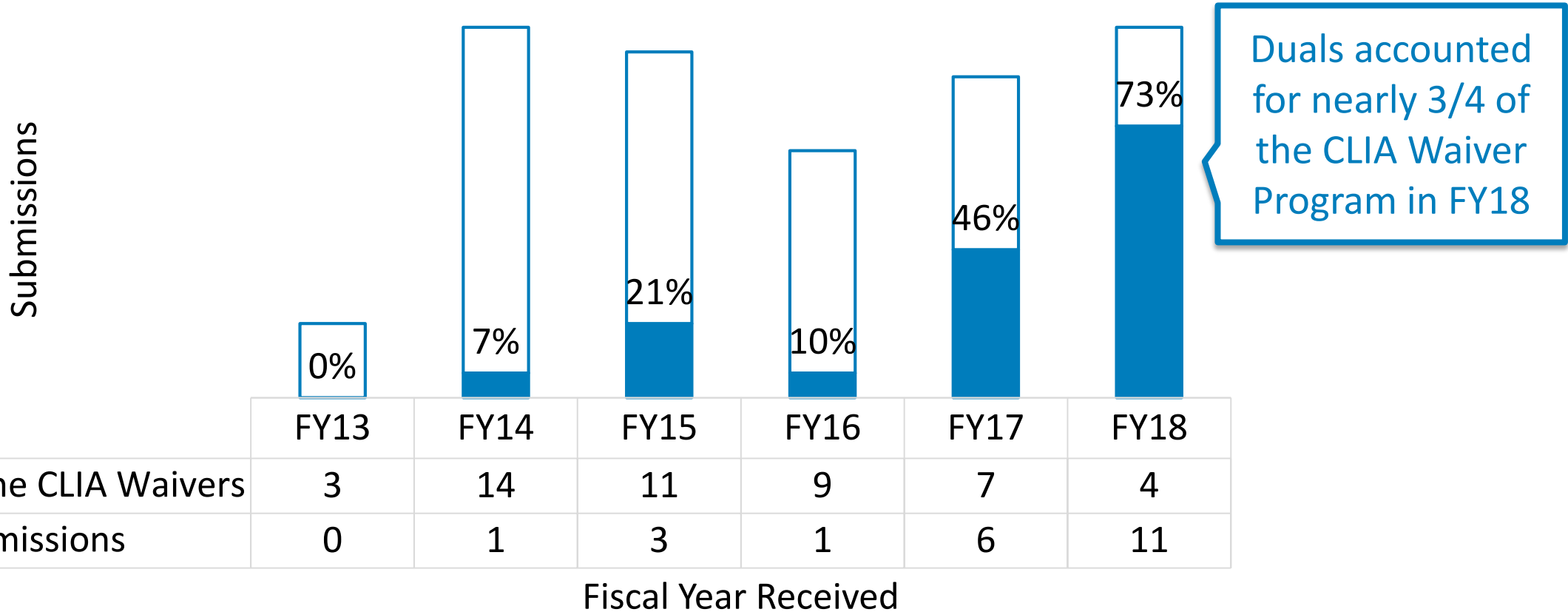
510(k) – POC

- Analytical studies as
 - analytical sensitivity,
 - analytical specificity,
 - linearity,
 - reagent stability,
 - sample stability, and so on
- ~~Comparison study
(POC sites & trained users)~~
- ~~Reproducibility study
(POC sites & trained users)~~

CLIA Waiver Application

- Simple,
 - Flex studies
- Comparison study
(CLIA waived sites and untrained users)
 - Reproducibility study
(CLIA waived sites and untrained users)

Dual Submissions Became the Preferred CLIA Waiver Pathway in FY18



Resources

- Draft guidances: **Please Comment (Due Feb 27, 2019)**
 - [Select Updates for Recommendations for Clinical Laboratory Improvement Amendments of 1988 \(CLIA\) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices; Draft Guidance for Industry and FDA Staff, Comment Here: FDA-2017-D-5570](#)
 - [Recommendations for Dual 510\(k\) and CLIA Waiver by Application Studies; Draft Guidance for Industry and FDA Staff, Comment Here: FDA-2017-D-5625](#)
- Final guidances:
 - [Recommendations for Clinical Laboratory Improvement Amendments of 1988 \(CLIA\) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices](#)
 - [Administrative Procedures for CLIA Categorization](#)
- [CLIA Waiver Decision Summaries](#)

Questions?

CLIA@fda.hhs.gov

Slide Presentation, Transcript and Webinar
Recording will be available at:

<http://www.fda.gov/training/cdrhlearn>

Under the Heading: In Vitro Diagnostics